



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

By Certified Mail – Return Receipt Requested
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CBER – 02 – 016

Warning Letter

SEP 27 2002

Eddy C. Hsueh, M.D.
John Wayne Cancer Institute
2200 Santa Monica Boulevard
Santa Monica, California 90404

Dear Dr. Hsueh:

During an inspection that ended on April 23, 2002, Ronald L. Koller, an investigator with the Food and Drug Administration (FDA), reviewed your activities as a clinical investigator testing an investigational melanoma vaccine. The studies are _____ and _____ (hereafter referred to as _____ and _____ respectively). The inspection was conducted as part of the FDA's Bioresearch Monitoring Program that includes inspections designed to review the conduct of clinical research involving investigational drugs.

Based on the inspection, we have determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations (CFR), Part 312 (available at <http://www.access.gpo.gov/nara/cfr/index.html>). The violations were detailed in Form FDA-483 presented to you at the close of the inspection. We have reviewed your May 30, 2002, response to the Form FDA-483. Your response does not describe corrective actions adequate to ensure that the violations cited in the Form FDA-483 have been addressed. Significant violations cited during the inspection and our comments on your response are provided below.

1. **You failed to protect the rights, safety, and welfare of study subjects.**
[21 CFR § 312.60 and Part 50].

You failed to use the most current version of the IRB approved consent form when you obtained the written consent from the following subjects.
Furthermore, you did not use the correct study consent form for two subjects.

Subject	Study	Date signed	Date of the most recent IRB approval	Version signed (date of IRB approval)
_____	_____	4-20-00	3-20-00	11-3-99
_____	_____	6-6-00	3-20-00	11-3-99
_____	_____	12-1-00	3-20-00	8-22-00 *
_____	_____			This is the consent form for another study
_____	_____	6-22-00	3-20-00	9-13-99
_____	_____	12-20-00	8-22-00	10-4-00 *
				This is the consent form for another study

Your response letter states that in the future you will remove older versions of the consent forms after the most recent version is approved.

Your response letter does not describe corrective actions to ensure that subjects who signed consent forms for a different study will be properly informed. In addition, your response does not describe any corrective action to ensure that the proper consent form is available and used.

2. You failed to ensure that the investigation is conducted according to the investigational plan. [21 CFR § 312.60].

- A. Section 11.1.4 in protocol _____ states: "...it is important that the individual preparing the study drugs must be someone other than the person administering the vaccine" and "It will still be necessary, however, for the investigational agent to be reconstituted and blinded by a third party who will have no role in the management of the patient or assessment of toxicity."

On several occasions, personnel who prepared the study drug subsequently administered study drug injections and conducted study-related assessments. The following are examples.

- i. _____ - On 3/7/00, staff member _____ prepared the study drug. On 5/30/00, 9/19/00, 11/16/00, and 6/12/01, _____ administered additional injections of study drug and conducted study assessments.
- ii. _____ - On 4/11/00 and 5/8/00, staff member _____ prepared the study drug. On 6/7/00, 7/6/00, 8/2/00, and 8/30/00, _____ administered additional injections of study drug and conduct study assessments.

Your response letter acknowledges these violations. You state that on 6/9/2000 you adopted the new Policy/Procedure # 3W-004 to prevent the unblinding of the study, yet the examples cited above illustrate that the procedure was in place, but was not followed. Your response does not describe corrective actions to ensure that established policy and procedures will be followed.

- B. You administered a dose of expired study drug to subject _____. The study drug expired on 4/13/01, but the product was administered on 5/14/01.

Your response acknowledges this violation and states that the revised Policy/Procedure # 3W-002 requires the study drug preparer to check the expiration date while preparing the study drugs. Your response does not describe corrective actions to ensure that established policy and procedures will be followed. For example, your revised procedure could, but does not, include supervisory or peer review to ensure that steps required during drug preparation are properly followed.

- C. You failed to report serious adverse events (SAEs) according to the requirements established in the protocols. Section 17.3 of protocols _____ and _____ requires that all SAEs occurring while subjects are receiving study drug or within _____ days of receipt of the final dose of study drug are to be reported to the sponsor within _____ of their discovery. According to the protocols, SAEs include events that require inpatient hospitalization or result in death and any death attributed to the study treatment must be immediately reported to the sponsor as an SAE.

In addition, section 17.5 of these protocols requires "all serious adverse events must also be immediately reported in writing to the Institutional Review Board (IRB) or the Ethics Committee (EC) by the Investigator."

The table below includes examples in which you did not immediately report SAEs to the sponsor and the IRB.

Subject	SAE	Onset date	Date Dr. Hsueh was notified	Date sponsor notified	Date IRB notified
_____	Hospitalized	7/13/00	7/27/00	8/31/00	8/31/00
_____	Death				
_____	Ruptured disc – laminectomy	9/26/00	1/19/01	1/24/01	1/30/01

Your response attributes these violations to your previous misunderstanding that events related to recurrence or progression of melanoma disease did not require SAE reports. Your response does not describe corrective actions to ensure that reporting requirements specified by the IRBs and in the protocols will be followed.

- D The protocol _____ site reference manual requires "A written Informed Consent Form signed by the patient and the Investigator or Investigator's designee...If the site IRB requires a witness signature, the witness must personally sign and date the informed consent the **same day** as the patient" (emphasis in original). The consent form approved by the Institutional Review Board requires a witness signature. The consent form signed by subjects _____ and _____ lack the signature of a witness, and the form signed by _____ lacks the signature of the investigator or investigator's designee.

Your response letter acknowledges these errors, but explains that these subjects were later determined not to be eligible for the study. The fact that individuals were subsequently found not to be eligible for the study does not negate these violations. The process of informed consent is separate and distinct from the process of qualifying potential study subjects. Your response does not state whether or how you will implement corrective actions to ensure that informed consent will be properly provided and obtained.

- E. Some protocol-required tests were not performed, including the following:

- i Laboratory tests on day 56 for Subject _____
- ii. Chest x-ray on month 12 for Subject _____
- iii. Vaccine skin test for Subject _____ on 11/20/00.

Your response acknowledges these violations, and includes new Policy/Procedures # 3W-001 and # 3W-013 to ensure that all required tests are performed. If followed, these procedures appear to be adequate to correct these violations.

- F. The "Site Reference Manuals" for protocols _____ and _____ state "Laboratory test results must be initialed and dated by the Investigator indicating that they were reviewed." There are several laboratory reports that were not signed or dated by you or a sub-investigator responsible to you. Examples include, but are not limited to, the following:

Subject _____ report dated 11/16/00), Subject _____ (report dated 1/29/01), Subject _____ (report dated 5/21/01), and Subject _____ (report dated 12/13/01).

Your response agrees with this observation, and describes that you implemented Policy/Procedure # 3W-005 on 8/29/00. We note that each of the above examples occurred after you implemented # 3W-005. Your response does not describe corrective actions to ensure that established policy and procedures will be followed. For example, your procedures could, but do not, include supervisory or peer review to ensure that each step in the procedure has been properly executed or completed.

Furthermore, we note that this new procedure, # 3W-005, appears inconsistent with the protocol requirements. The procedure requires the study nurse to review all laboratory reports and to present abnormal laboratory reports to the clinical investigator for consideration. However, the protocol requires the clinical investigator's signature and date on all laboratory reports. You provide no justification, nor can we think of a reason, for implementing a procedure that is inconsistent with protocol requirements.

- G The protocol requires that corrections to case report form data may be made only by putting a single line through the incorrect data, and then writing the correct data, the initials of the person making the change, and the date. This procedure was not followed on many records, including study visit notes and drug accountability records. Sometimes the initials and date were omitted, and sometimes the original data was written over

Your response states that you have implemented additional training of study personnel. Your response appears to be adequate.

3. You failed to report all unanticipated problems involving risks to human subjects to the Institutional Review Board. [21 CFR § 312.66].

In letters to you dated 5/4/00, 10/6/00, 7/11/01, 9/5/01, and 11/8/01, the IRB states "Any death of a patient on protocol regardless of cause, must be reported in writing to the IRB within _____ after discovery. All serious and/or unexpected, as defined on the IRB reporting form, adverse events must be reported to the IRB in writing within - calendar days after discovery."

You failed to meet these requirements when reporting the adverse events identified in item 2B above.

In your response, you attribute these violations to your misunderstanding of the definition of a serious adverse event. Your response provides Policy/Procedure # 3W-009 for reporting adverse events related to the investigational melanoma vaccine studies of one sponsor. We note that this procedure may not be applicable to other study protocols for this sponsor or other sponsors. Your response, therefore, does not describe corrective actions adequate to ensure that SAE's will be properly reported.

**4. You failed to maintain adequate records of the disposition of the drug.
[21 CFR § 312.62(a)].**

- A. Drug accountability records contain inaccuracies. On at least three dates, the test article accountability records show that the test article was prepared the day after it was administered, as follows:

Subject	Preparation date	Administration date
_____	9/15/00	9/12/00
_____	5/5/01	5/4/01
_____	11/4/01	11/3/01

- B. The "Vaccine Preparation & Administration Log" records that Subject _____ was administered vaccine on 4/6/00, but the "Investigational Accountability Record" states the vaccine was administered on 4/7/00.

Your response attributes these violations as "very likely the result of erroneous date entry." You state that you revised Policy/Procedure # 3W-002. We note that two of the errors noted above occurred despite an earlier version of this policy/procedure that directed staff to document the dates of preparation and administration. Your response does not describe corrective actions to ensure that established policy and procedures will be followed. For example, your procedures could, but do not, include supervisory or peer review to ensure that each step in the procedure has been properly executed or completed.

**5. You failed to maintain adequate and accurate case histories.
[21 CFR § 312.62(b)].**

Protocols _____ and _____ require that the study drug must be administered to subjects within _____ minutes after it is thawed. On at least ten occasions, the time the drug was administered is not documented in the "Vaccine Preparation & Administration Log" designed for that purpose.

Your response attributes these violations to a lack of training by the study drug preparer, and claims that Policy/Procedure # 3W-002 will prevent the problem in the future. Your response does not describe how you will ensure that established policy and procedures will be followed.

Many of the deficiencies noted above have continued to occur despite repeated monitoring of these protocols by the sponsor and the sponsor's instructions to you to implement corrections. Your response does not describe corrective actions generally to ensure that policy and procedures will be followed.

You submitted several new Standard Operating Procedures (SOPs) as part of your response letter. Some of these SOPs, shown as "approved" under your signature, state that they apply to "all Investigators and Clinical Research Nurses participating in JWCI [John Wayne Cancer Institute] clinical trials" (# 3W-010), "all JWCI Clinical Research Nurses and Data Coordinators" (# 3W-011 and # 3W-013), or "all Clinical Research Nurses participating in JWCI clinical trials" (# 3W-012). This language indicates that these SOPs apply to studies for which you are not the clinical investigator, and those where you are not in a position of authority. These SOPs do not appear to have been approved. Unless they are revised to be specific for only the studies under your direct supervision, or unless these SOPs have been reviewed and approved by authorized JWCI officials, they appear inadequate to address the deficiencies.

This letter is not intended to be an all-inclusive list of deficiencies. Several violations noted during the inspection are not enumerated in this letter because they occurred before you assumed responsibility for the conduct of the studies. However, your response acknowledges those violations and promises to ensure that they do not reoccur. Your corrective actions are subject to verification in future inspections. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations.

Please notify this office, in writing, within fifteen (15) business days after receipt of this letter, of the specific actions you have taken to correct the noted violations, including an explanation of each step you plan to take to prevent a recurrence of similar violations. If corrective action cannot be completed within fifteen (15) business days, state the reason for the delay and the time within which the corrections will be completed. Your response should include any documentation necessary to show that correction has been achieved.

Failure to promptly correct these deviations may result in enforcement action without further notice. Please also be advised that the failure to effectively put into practice the corrective actions you have described in your response letter, or the commission of other violations, may result in the initiation of enforcement action(s) without further notice. These actions could include: placing on clinical hold trials that involve current subjects; initiating investigator disqualification proceedings, which may render a clinical investigator ineligible to receive investigational new drugs; and initiating an action for injunction.

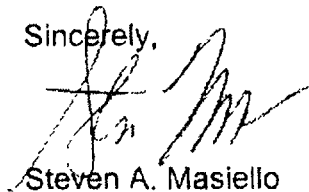
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Please send your written response to:

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1401 Rockville Pike, Suite 200N
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Telephone: (301) 827-6221

We request that you send a copy of your response to the Food and Drug Administration's Los Angeles District Office listed below.

Sincerely,



Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc: Alonza E. Cruz, Director
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